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Research Article

Self-reported sleep disturbance is associated with Alzheimer's disease risk in men

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Abstract

Objective: To study the association between self-reported sleep disturbances and dementia risk.
Methods: Self-reported sleep disturbances and established risk factors for dementia were measured in men at ages 50 (n = 1574) and 70 (n = 1029) years. Dementia incidence was determined by reviewing their patient history between ages 50 and 90 years. In addition, plasma levels of β-amyloid (Aβ) peptides 1–40 and 1–42 were measured at ages 70, 77, and 82 years.
Results: Cox regression demonstrated that men with self-reported sleep disturbances had a higher risk of developing dementia (+33%) and Alzheimer's disease (AD, +51%) than men without self-reported sleep disturbances (both $P < .05$). Binary logistic regression showed the increased risk for both dementia (+114%) and AD (+192%) were highest when sleep disturbance was reported at age 70 years (both $P < .001$). No group differences were found in Aβ levels.
Conclusion: Improving sleep quality may help reduce the neurodegenerative risk in older men.

Keywords: Sleep; All-cause dementia; Alzheimer's disease; Longitudinal study

1. Introduction

Experimental studies in both animals and humans have demonstrated that insufficient sleep exerts considerable effects on brain health. When awake, there is a normal accumulation of toxic substances in the brain of mice. Using convective flow between the cerebrospinal fluid and interstitial fluid, these toxic metabolites are removed from the murine brain during subsequent sleep, thereby ensuring that the neuronal exposure to neurodegenerative factors is kept at a minimum [1]. Of note, clearance during sleep was as much as twofold faster than during waking hours in this study [1], indicating that a normal night's sleep may be critical for maintaining brain health in mice, and, most likely, also in humans. In line with these findings, we have recently demonstrated in healthy young men [2] that one night of total sleep deprivation increases morning blood concentrations of neuron-specific enolase (NSE)—an enzyme found in all neurons [3]—and S100 calcium binding protein B (S-100B)—a protein which is mainly found in the glial cells of the peripheral and central nervous system [4]. As these brain metabolites typically rise in blood under conditions of neurodegeneration [5,6], these results also indicate that a lack of sleep may be harmful for the brain. Finally, in a cross-sectional study of 70 adults (mean age 76 years, range 53–91 years) from the neuroimaging substudy of the Baltimore Longitudinal Study of Aging, it has been shown that self-reported shorter sleep duration was associated with

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greater β-amyloid (Aβ) burden in the brain [7]. The aggregation of Aβ in the brain is hypothesized to be linked to neurodegenerative processes, most notably in Alzheimer disease (AD) [8].

Against this background, the present study, involving 1574 men at age 50 years with a mean follow-up of ~40 years, aimed to ascertain if reports of sleep disturbances were associated with an increased risk to develop all-cause dementia. In addition, we examined if reports of sleep disturbances were linked to changes in plasma levels of Aβ peptides 1–40 and 1–42.

2. Methods

2.1. Patient population

The Uppsala Longitudinal Study of Adult Men (ULSAM) was initiated in 1970. All 50-year-old men born between 1920 and 1924 and living in Uppsala, Sweden, were invited to participate in a health survey aimed at identifying cardiovascular risk factors ([9]; see also http://www.pubcare.uu.se/ULSAM). Of the 2841 invited men, 82% (2322 men) participated in the investigation. Following the baseline investigation at age 50 years, subjects were re-examined at ages 60, 70, 77, 82, and 88 years. To examine the associations of self-reported sleep disturbances with all-cause dementia risk, a total of 1574 participants who had available follow-up data were entered into the present analysis (~68% of the men who participated in the baseline investigation; Fig. 1). In a subsample of those 1574 men, plasma levels of Aβ peptides 1–40 and 1–42 were determined at ages 70, 77, and 82 years (Fig. 1). These data were used to ascertain the association between plasma levels of Aβ peptides 1–40, 1–42, and their ratio, with self-reported sleep disturbance at age 70 years. All participants gave their informed consent and the Ethics Committee of Uppsala University approved the study.

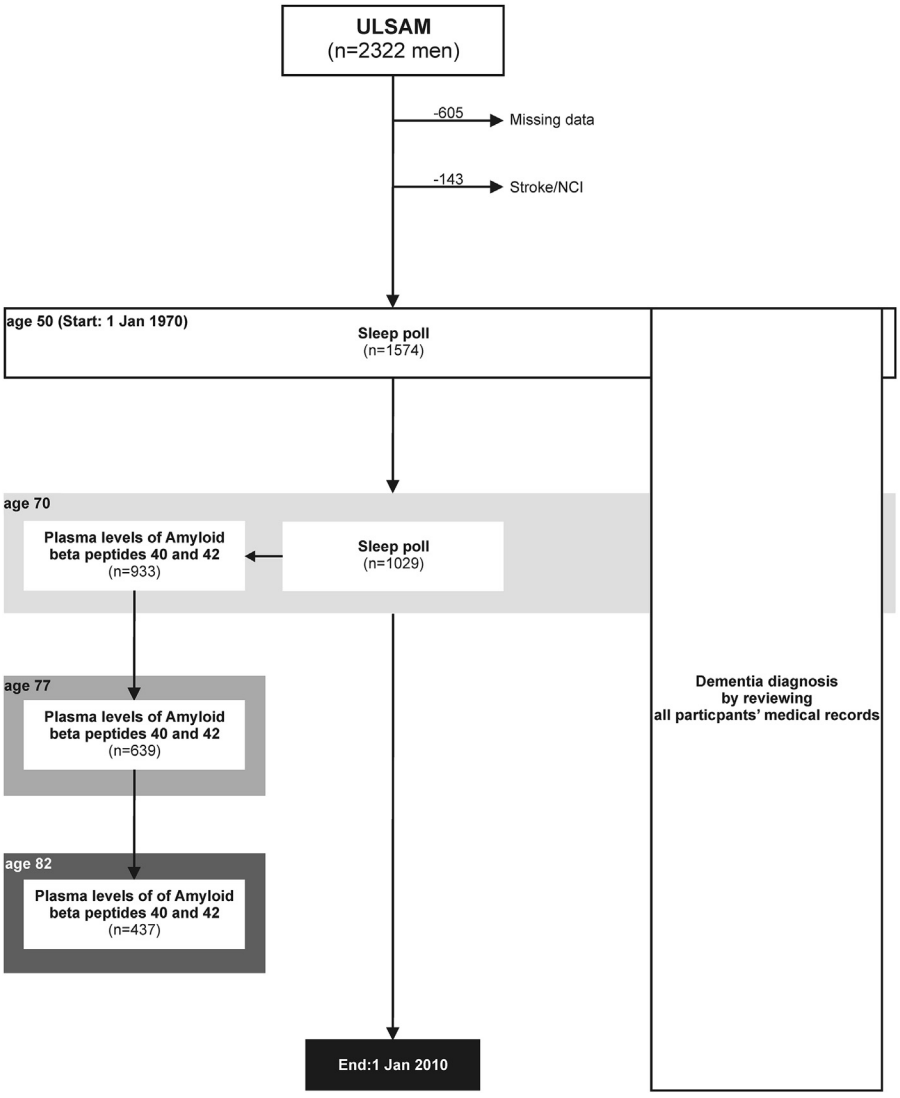

Fig. 1. Flowchart: Uppsala Longitudinal Study of Adult Men (ULSAM). NCI, not cognitively intact, which means evidence of cognitive impairment but data are insufficient and allows no further classification.

2.2. Primary exposure variable

At ages 50 and 70 years, participants were administered three sleep-related questions which could be answered either "no" or "yes": Do you have difficulties falling asleep at night?, Do you often wake up in the early hours, unable to get back to sleep?, and Do you take sleeping pills more than 3 times per week?. Answering "yes" to any of the three questions was herein considered to demonstrate that the participant at the time of the survey was likely to have a sleep disturbance. Thus, the three questions were combined into one variable (denoted "sleep disturbance"), which was given the value of 1 (present) if any of the three questions were answered as "yes" (i.e. a score of 1–3) and 0 (absent) otherwise (score 0). No established standardized questionnaires about sleep disturbances were available at the time of the baseline examination.

2.3. Primary outcome variable

The primary end point was the diagnosis of dementia. Dementia was assessed as described earlier [10]. Briefly, the medical records of the ULSAM participants from all the clinics of Uppsala University Hospital, the Uppsala general practitioners and nursing homes, were reviewed until January 1, 2010. Practically all medical care for the participants had been provided in these settings. The diagnoses of dementia were assigned by two experienced geriatricians independently, blinded from the baseline data, using all available data from these records. In the case of disagreement, a third experienced geriatrician reviewed the case and the diagnosis was determined by majority decision. Dementia was diagnosed according to the criteria from *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) [11]. A poststroke status with major motor sequelae and/or aphasia precluding neuropsychological testing and/or inferring a major impact on daily functions (stable over time) was not classified as dementia. AD was diagnosed according to the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's disease and Related Disorders Association criteria [12]. A detailed description of cognitive decline over time (excluding deterioration in connection with possible brain ischemia) and relevant cognitive testing were mandatory prerequisites for a diagnosis of pure AD. In addition, magnetic resonance imaging or computed tomography scanning showing either a normal picture or atrophy, no more than one clinically silent infarction, and no more than mild white matter lesion were required for a diagnosis of pure AD. Vascular dementia was diagnosed according to the Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) core criteria [13], frontotemporal dementia according to the McKhann criteria [14] and Lewy body dementia according to the McKeith criteria [15]. A diagnosis of mixed dementia was made when both AD and cerebrovascular disease were considered to contribute to dementia. Cases of dementia without neuroimaging and without sufficient clinical details in the medical records to set a specific dementia subtype diagnosis were classified as unspecified dementia.

2.4. Laboratory assessment

We analyzed Aβ 1–40 and Aβ 1–42 levels in plasma using a well-characterized enzyme-linked immunosorbent assay method with BNT77 (IgA mouse anti-Aβ11-28; Takeda, Osaka, Japan) and horseradish peroxidase-conjugated detector antibodies (BA27, IgG2 mouse anti-Aβ40; and BC05, IgG1 mouse anti-Aβ42; Takeda), as previously described [16]. We analyzed Aβ40 in duplicate and Aβ42 in triplicate samples.

2.5. Covariates

Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared (kg/m^2). The presence of elevated blood pressure was defined as systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg, and/or use of antihypertensive medication. The presence of diabetes was defined as fasting blood glucose $\geq$6.1 mmol/l and/or use of oral hypoglycemic agents or insulin. Leisure-time physical activity was assessed as previously described [17]. Briefly, the following questions were administered to the participants: Do you spend most of your time with reading, watching television, going to the cinema, or engaging in other, mostly?, Do you often go walking or cycling for pleasure?, Do you engage in any active recreational sports or heavy gardening for at least 3 hours every week?, and Do you regularly engage in hard physical training or competitive sport?. The highest positive physical activity response level was used for each participant. Education level was stratified as low (elementary school), medium (high school), or high (college studies or higher).

2.6. Statistical analysis

To explore the association between self-reported sleep disturbance and dementia, a cox regression analysis was chosen. The Cox regression analysis used time-updated exposure and covariate information (i.e. the variables were measured at ages 50 and 70). Time at risk was calculated from exact age to the age of dementia diagnosis, death, or age at end of follow-up (January 1, 2010), whichever came first. Dates of death were obtained from the continuously updated cause of death register held by the National Board of Health and Welfare in Sweden. The associations of self-reported sleep disturbance (categorical variable) with dementia were investigated using three multivariable models. Model A was adjusted for exact age (continuous variable), model B for lifestyle factors (Model A+ body mass index (continuous variable), leisure-time physical activity (categorical variable) and

education level (categorical variable)), and model C for cardiometabolic risk factors (Model B + hypertension (categorical variable) and diabetes (categorical variable)). Proportional hazards assumptions were confirmed using graphical evaluation. A linear mixed model was used to analyze the associations between plasma levels of Aβ peptides 1–40, 1–42, and their ratio with sleep disturbance at age 70 years. A two-sided *P*-value of less than .05 was regarded as statistically significant in all analyses. For all analyses, SPSS statistical software package was used (version 20.0; SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Descriptive

Characteristics, stratified by self-reported sleep disturbance at ages 50 and 70 years, are shown in Table 1. At age 50 years, men with self-reported sleep disturbance were more often diagnosed with hypertension (or received an antihypertensive treatment) and diabetes (or received an antidiabetic treatment) than men without self-reported sleep disturbances (hypertension: $\chi^2 = 5.96$, df = 1, $P = .01$; diabetes: $\chi^2 = 4.83$, df = 1, $P = .03$). Compared with men in the group "No Sleep Disturbance", those who had a sleep disturbance at age 50 years reported to be less physically active during leisure time ($\chi^2 = 15.24$, df = 3, $P = .002$). At age 70 years, it was observed that the BMI of men with a sleep disturbance at age 70 years slightly exceeded that of men without sleep disturbance (t = −2.70, df = 1027, $P = .007$, independent Students' *t* test).

Table 1
Characteristics, stratified by self-reported sleep disturbance at ages 50 and 70 years, among participants in the Uppsala Longitudinal Study of Adult Men (ULSAM)

	Age 50		Age 70	
Characteristic	Sleep disturbance	No sleep disturbance	Sleep disturbance	No sleep disturbance
Persons at risk, n	342	1232	236	793
Age, yr, mean (SD)	49.6 (0.6)	49.6 (0.6)	71.0 (.6)	71.0 (.5)
BMI, kg/m^2, mean (SD)	25.0 (3.1)	25.1 (3.2)	26.7 (3.9)	26.1 (3.2)
Leisure-time PA, n (%)				
Sedentary	59 (17)	163 (13)	11 (5)	31 (4)
Moderate	136 (40)	431 (35)	93 (39)	264 (33)
Regular	123 (36)	581 (47)	124 (53)	452 (57)
Athletic	24 (7)	57 (5)	8 (3)	46 (6)
Educational level, n (%)				
Primary school	206 (60)	778 (63)	133 (56)	447 (56)
Secondary school	90 (26)	321 (26)	60 (25)	233 (29)
University	46 (13)	133 (11)	43 (18)	113 (14)
Diabetes, n (%)				
Yes	9 (3)	13 (1)	38 (16)	99 (12)
No	333 (97)	1219 (99)	198 (84)	694 (88)
Hypertension, n (%)				
Yes	84 (25)	229 (19)	85 (36)	240 (30)
No	258 (75)	1003 (81)	151 (64)	553 (70)

Abbreviations: SD, standard deviation; BMI, body mass index; PA, physical activity.

3.2. Self-reported sleep disturbance and dementia risk

In total, the investigated cohort was totally 35.380 years at risk. Multivariate Cox regression analysis using time-updated exposure and covariate information demonstrated that men with self-reported sleep disturbances had a ∼1.33-times higher risk to develop all-cause dementia during the 40-year observation period when compared with men without self-reported sleep disturbances (Table 2). This association was most pronounced for AD (+51%; Table 2). No significant interactions of the primary effector variable self-reported sleep disturbance with the covariates education, BMI, diabetes, hypertension, leisure-time physical activity were obtained by the Cox regression analysis ($P \geq .17$ for all interaction terms).

A univariate binary logistic regression was then used to explore whether the degree of self-reported sleep disturbances (i.e. either no self-reported sleep disturbance at all (69% of the cohort), self-reported sleep disturbance only at age 50 (16%), self-reported sleep disturbance only at age 70 (9%), or self-reported sleep disturbance at both ages (6%)) would predict the risk for all-cause dementia. This analysis revealed that men with self-reported sleep disturbances at age 70 years exhibited the highest risk to develop all-cause dementia (odds ratio [OR] [95% confidence interval (CI)]; 2.14 [1.42,3.21], $P < .001$), compared with men without sleep disturbances. In contrast, those who reported a sleep disturbance at age 50 years did not have a higher risk to develop all-cause dementia than those without sleep disturbances (OR [95%CI]; 0.84 [0.56,1.26], $P = .39$). Similar results were found for the relative risk to develop AD (OR [95%CI]; men with self-reported sleep disturbance at age 70 years: 2.92 [1.76,4.87], $P < .001$; men with self-reported sleep disturbance at age 50: 0.98 [0.42,2.33], $P = .98$). Self-reported sleep disturbances at both ages did not explain additional variance of the observed associations.

3.3. Plasma levels of Aβ peptides 40, 42, and their ratio

Utilizing a linear mixed model that was controlled for potential confounders at age 70 years (i.e. physical activity, educational level, BMI, diabetes state, and hypertension state), no significant differences were found between reports of sleep disturbance at age 70 years and plasma levels of Aβ peptides 1–40/1–42 measured at ages 70, 77, and 82 years ($P \geq .11$ for all sleep main effects and sleep*time interaction effects; Fig. 2).

4. Discussion

We demonstrate that reports of sleep disturbances were associated with an increased risk to develop all-cause dementia in initially cognitively healthy men during a 40-year observation period. Of note, this association was

Table 2
Association between self-reported sleep disturbances and dementia risk in the Uppsala Longitudinal Study of Adult Men (ULSAM)

Characteristic	Sleep disturbance	No sleep disturbance	Model	HR (95% CI)	*P*
Persons at risk					
Age 50	342	1232	–	–	–
Age 70	236	793	–	–	–
All-cause dementia, n (%) baseline)	72 (21)	198 (16)	A	1.33 (1.01–1.74)	.04
	-"-	-"-	B	1.34 (1.02–1.76)	**.03**
	-"-	-"-	C	1.33 (1.01–1.75)	**.04**
AD, n (% of all-cause dementia)	34 (47)	85 (43)	A	1.44 (0.97–2.14)	.07
	-"-	-"-	B	1.51 (1.01–2.25)	**<.05**
	-"-	-"-	C	1.51 (1.01–2.25)	**<.05**
VaD, n (% of all-cause dementia)	16 (22)	45 (23)	A	1.30 (0.73–2.30)	.37
	-"-	-"-	B	1.26 (0.71–2.24)	.44
	-"-	-"-	C	1.23 (0.69–2.20)	.48
AD–VaD, n (% of all-cause dementia)	4 (6)	9 (5)	A	1.62 (0.50–5.28)	.42
	-"-	-"-	B	1.64 (0.50–5.34)	.41
	-"-	-"-	C	1.78 (0.54–5.86)	.35
FTD, n (% of all-cause dementia)	2 (3)	4 (2)	A	1.87 (0.34–10.23)	.47
	-"-	-"-	B	1.75 (0.32–9.67)	.52
	-"-	-"-	C	1.76 (0.32–9.82)	.52
PDD/LBD, n (% of all-cause dementia)	3 (4)	11 (6)	A	1.01 (0.28–3.63)	.99
	-"-	-"-	B	0.88 (0.24–3.25)	.85
	-"-	-"-	C	0.85 (0.23–3.16)	.81
UND, n (% of all-cause dementia)	13 (18)	44 (22)	A	1.09 (0.59–2.03)	.78
	-"-	-"-	B	1.14 (0.61–2.13)	.68
	-"-	-"-	C	1.13 (0.60–2.10)	.71

Abbreviations: HR, hazard ratio; CI, confidence interval; cont., continuous; cat., categorical; AD, Alzheimer's disease; VaD, vascular dementia; FTD, frontotemporal dementia; PDD/LBD, Lewy body dementia; UND, unspecified dementia.

NOTE. Time at risk was calculated from exact age at first examination to the date of dementia diagnosis, death, or end of follow-up, whichever came first. The Cox regression analysis used time-updated exposure and covariate information.

Bold values indicate statistical significance (ie: $P < 0.05$).

Model A indicates model adjusted for age.

Model B indicates lifestyle model (age, body mass index [cont.], leisure-time physical activity [cat.], and educational level [cat.]).

Model C was additionally adjusted for cardiometabolic factors (Model B + hypertension [cat.] and diabetes [cat.]).

strongest for AD. In contrast, plasma levels of Aβ peptides 1–40 and 1–42 were not different between those who reported to have a sleep disturbance and those who did not. These community-based data confirm and extend previous experimental and epidemiological research [1,2,18–20] that suggest that getting a regular good night's sleep may be a useful means for supporting long-term brain health in humans.

4.1. Comparison with literature

A recent longitudinal study using data from a population-based sample of 214 Swedish adults aged 75 years and over demonstrated that reduced sleep duration was associated with a 75% increased all-cause dementia risk and double the risk of AD [20]. Similar but weaker associations were observed in the present study. That the strength of our association is less pronounced than that observed in the prior study by Hahn et al. may be explained by differences in the sample size (ours vs. Hahn's study: 1606 vs. 214), gender distribution (100% males vs. 80%/20% females/males), length of observation period (40 years vs. 9 years), the number of sleep disturbance assessments (baseline and age 70 years vs. baseline), clinical characteristics of the study samples, and age at entry (50 years vs. 83 years). Supporting the view that especially age may modulate the strength of the association between sleep disturbances and dementia risk, we found that men with self-reported sleep disturbances at age 70 years but not 50 years had a twofold higher risk to develop dementia and a threefold higher risk to develop AD, than those without any sleep disturbance. A possible explanation could be that the ability of the aged brain to clean itself from neurotoxic substances during sleep might be more attenuated than at a younger age when sleep is disturbed.

Another finding of our study is that reported sleep disturbance at age 70 years was neither linked to plasma levels of Aβ peptides 1–40 and 1–42 measured at the same age, nor at a later time point. At first glance, these results contrast previous findings. For instance, by analyzing CSF from 145 cognitively normal individuals who were 45 years and older, researchers were able to demonstrate that CSF Aβ 1–42 levels were lower in those who have objectively (i.e. measured by wrist actigraphy) lower sleep quality [19]. Moreover, as mentioned earlier, self-reported shorter sleep duration has been associated with greater Aβ burden in the brain of 70 elderly subjects [7]. Several reasons may have masked possible effects on Aβ peptides 1–40 and 1–42. First, plasma may be less sensitive than CSF to reflect a

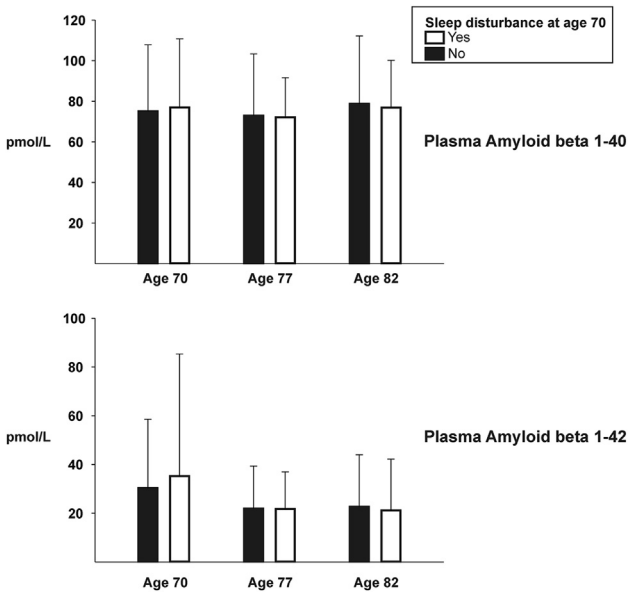

Fig. 2. No significant differences in plasma amyloid beta peptides (measured at ages 70, 77, and 82 years) between men with and without self-reported sleep disturbance at age 70 years. Data are mean ± standard deviation.

potential impact of perceived sleep disturbance on Aβ peptides. Second, plasma levels of Aβ peptides were measured at ages 70, 77, and 82 years. Bearing in mind that plasma Aβ peptides usually increase before the onset of dementia but decrease thereafter [21], we cannot rule out that the chosen blood sampling frequency may not have captured possible differences in plasma levels of Aβ peptides 1–40 and 1–42 between the groups with and without reported sleep disturbances. Finally, it must be noted that the use of plasma Aβ peptides 1–40 and 1–42 to predict reliably the transition of cognitive decline to AD is subject of ongoing scientific debate [22,23].

4.2. Potential mechanisms for the observed associations

Our observational study is limited as we cannot yet establish causality. There are several potential pathways that may explain the association between reports of sleep disturbance and the risk to develop all-cause dementia and AD, respectively. Sleep represents a period during which brain glucose metabolism drops by ∼30%, compared with values obtained during wakefulness [24]. Substrate oxidation ultimately leads to the production of reactive oxygen species (ROS), such as hydrogen peroxide [25]. Previous experiments have demonstrated that ROS can damage neurons and even induce cell death [26]. Another possible interpretation could be, as described earlier, that poor sleep may lessen the ability of the brain to remove toxic substances [1], thereby increasing and prolonging the exposure of neurons to neurodegenerative factors, ultimately perhaps resulting in reversible or irreversible neuronal damage, depending on the length and degree of exposure to sleep deprivation. However, it is important to note that, as of yet, evidence is lacking that perceived lower-quality sleep may concur with a greater neurodegenerative load and/or a reduced ability of the brain to clear itself from toxic substances.

Importantly, it must be borne in mind that self-reported sleep disturbances, unlike a nocturnal polysomnography (NSPG), do not allow one to draw firm conclusions as to whether an individual's sleep architecture is healthy or not. Thus, it cannot be ruled out that self-reported sleep disturbances in our study were related to age-related changes in sleep patterns, poor sleep hygiene, and/or environmental sleep issues. In addition, self-reported sleep disturbances may be secondary to a primary disease (e.g. depression), which by itself increases the risk for neurodegenerative processes. Finally, men with sleep disturbances had more often hypertension, diabetes, and a higher BMI than men without sleep disturbances. Similar medical conditions are found in patients with sleep apnea [27–29]. Interestingly, this sleep disorder has recently been linked to neurodegenerative processes [30].

4.3. Strengths and limitations

The major strength of our investigation includes the long follow-up period (∼40 years). During aging, total sleep time, sleep efficiency, percentage of slow-wave sleep, percentage of rapid eye movement sleep, and rapid eye movement sleep latency all significantly decrease [31], indicating that repeated measures of sleep disturbance—as collected in the present study—help minimize the confounding effect of age on sleep quality. However, there are also several limitations that apply: A history of chronic insomnia does not per se predict poor sleep as determined by NSPG [32]. That said, our findings must be confirmed by prospective studies utilizing objective measures of sleep quality (e.g. actigraphy, NSPG). Nevertheless, the consistency of the association between reports of sleep disturbance and risk to develop dementia would argue against the results as chance findings. Moreover, it must be borne in mind that medical conditions that were not entered in the present analysis as possible confounders can adversely impact human sleep architecture (e.g. depression, e.g. as found by Hahn et al. [20]), and may therefore partly account for the observed association between sleep disturbance and dementia risk. Another limitation is the unknown generalizability to females and other geographical and ethnic groups. Finally, confounds by other factors, such as genetic background (e.g. apolipoprotein E [33];), that were not considered in the present analysis, cannot be excluded.

5. Conclusion

Approximately every other adult in North America reports the quality of their nighttime sleep as being insufficient [34]. Furthermore, insomnia and decreased sleep quality are typical attending ills of many widespread diseases in modern societies (e.g. diabetes, hypertension, and obesity) [35–38].

Thus, in our view our findings are relevant for both the public and healthcare practitioners, as they suggest that strategies aimed at improving sleep quality (e.g. regular exercise) may help reduce the neurodegenerative risk for a significant proportion of our society.

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RESEARCH IN CONTEXT

1. Systematic review: We searched reports from cohort studies to identify studies reporting on the epidemiology of sleep disturbances and dementia risk. Except for several cross-sectional studies (e.g. involving neuroimaging techniques), no longitudinal study with a follow-up period that was similar to ours (i.e. 40 years) was identified.
2. Interpretation: We demonstrate that reports of sleep disturbances were associated with an increased risk to develop all-cause dementia and Alzheimer's disease in initially cognitively healthy men during a 40-year observation period. These findings could be relevant for both the public and healthcare practitioners, as they suggest that strategies aimed at improving sleep quality (e.g. exercise) may help reduce the neurodegenerative risk of elderly men.
3. Future directions: Studies utilizing methods that objectively measure sleep (e.g. nocturnal polysomnography) will help to further our understanding as to why poor sleep patterns increases our risk to develop neurodegenerative diseases. In this context, interventional studies with the intention of improving sleep patterns will be necessary to test whether such interventions can reduce the risk of developing neurodegenerative diseases and thus perhaps maintain cognitive health into older age.

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